Proposed Registration Decision PRD2015-21

# (S)-Methoprene

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# Table of Contents


Overview ..... 1
Proposed Registration Decision for (S)-Methoprene ..... 1
What Does Health Canada Consider When Making a Registration Decision? ..... 1
What Is (S)-Methoprene? ..... 2
Health Considerations ..... 2
Environmental Considerations ..... 4
Value Considerations ..... 4
Measures to Minimize Risk ..... 4
Next Steps ..... 5
Other Information ..... 5
Science Evaluation ..... 7
1.0 The Active Ingredient, Its Properties and Uses ..... 7
1.1 Identity of the Active Ingredient ..... 7
1.2 Physical and Chemical Properties of the Active Ingredient, Manufacturing Concentrate, and End-Use Product ..... 7
1.3 Directions for Use ..... 8
1.4 Mode of Action ..... 9
2.0 Methods of Analysis ..... 9
2.1 Methods for Analysis of the Active Ingredient ..... 9
2.2 Method for Formulation Analysis ..... 9
2.3 Methods for Residue Analysis ..... 9
3.0 Impact on Human and Animal Health ..... 9
3.1 Toxicology Summary ..... 9
3.1.1 *Pest Control Products Act* Hazard Characterization ..... 12
3.2 Acute Reference Dose (ARfD) ..... 13
3.3 Acceptable Daily Intake (ADI) ..... 13
3.4 Occupational and Residential Risk Assessment ..... 14
3.4.1 Toxicological Endpoints ..... 14
3.4.2 Occupational Exposure and Risk ..... 14
3.4.3 Residential Exposure and Risk Assessment ..... 17
3.5 Food Residues Exposure Assessment ..... 17
3.5.1 Residues in Animals ..... 17
3.5.2 Dietary Risk Assessment ..... 17
3.5.3 Aggregate Exposure and Risk ..... 17
3.5.4 Maximum Residue Limits ..... 18
4.0 Impact on the Environment ..... 18
4.1 Fate and Behaviour in the Environment ..... 18
4.2 Environmental Risk Characterization ..... 18
5.0 Value ..... 18
5.1 Consideration of Benefits ..... 18
5.2 Acceptable Claims and Effectiveness Against Pests ..... 19
5.3 Non-Safety Adverse Effects ..... 19

5.4 Supported Uses ..... 19
6.0 Pest Control Product Policy Considerations ..... 20
6.1 Toxic Substances Management Policy Considerations ..... 20
6.2 Formulants and Contaminants of Health or Environmental Concern ..... 20
7.0 Summary ..... 21
7.1 Human Health and Safety ..... 21
7.2 Environmental Risk ..... 21
7.3 Value ..... 22
8.0 Proposed Regulatory Decision ..... 22
List of Abbreviations ..... 23
Appendix I Tables and Figures ..... 25
Table 1 Residue Analysis ..... 25
Table 2a Toxicity Profile of the Product Altosid Beef Cattle Mineral ..... 25
Table 2b Toxicity Profile of the Manufacturing Use Product Altosid Beef 2% MUP ..... 26
Table 2c Toxicity Profile of Technical (S)-methoprene ..... 26
Table 3 Toxicology Endpoints for Use in Health Risk Assessment for (S)-methoprene ..... 38
Table 4 Integrated Food Residue Chemistry Summary ..... 38
Table 5 Food Residue Chemistry Overview of Metabolism Studies and Risk Assessment ..... 43
Appendix II Supplemental Maximum Residue Limit Information—International Situation and Trade Implications ..... 45
Table 1 Comparison of Canadian MRLs and Codex MRLs (where different) ..... 45
References ..... 47

# Overview

## Proposed Registration Decision for (S)-Methoprene

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of Precor Insect Growth Regulator, and Altosid Beef 2% MUP, containing the technical grade active ingredient (S)-methoprene. Altosid Beef 2% MUP will be used to manufacture the feed product Altosid Beef Cattle Mineral to control horn flies on beef cattle. Altosid Beef Cattle Mineral is exempt from registration under the *Pest Control Products Act* in accordance with paragraph 4(1)(b) of the Pest Control Product Regulations, and, more specifically, Schedule 2, Section 1.

An evaluation of available scientific information found that, under the approved conditions of use, the products have value and do not present an unacceptable risk to human health or the environment.

This Overview describes the key points of the evaluation, while the Science Evaluation provides detailed technical information on the human health, environmental and value assessments of Precor Insect Growth Regulator, and Altosid Beef 2% MUP.

## What Does Health Canada Consider When Making a Registration Decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks to people and the environment from the use of pest control products. Health or environmental risk is considered acceptable[1] if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its proposed conditions of registration. The Act also requires that products have value[2] when used according to the label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

To reach its decisions, the PMRA applies modern, rigorous risk-assessment methods and policies. These methods consider the unique characteristics of sensitive subpopulations in humans (for example, children) as well as organisms in the environment. These methods and policies also consider the nature of the effects observed and the uncertainties when predicting the impact of pesticides. For more information on how the PMRA regulates pesticides, the assessment process and risk-reduction programs, please visit the PMRA's website at healthcanada.gc.ca/pmra.

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1 *"Acceptable risks" as defined by subsection 2(2) of the Pest Control Products Act.*

2 *"Value" as defined by subsection 2(1) of the Pest Control Products Act: "the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's (a) efficacy; (b) effect on host organisms in connection with which it is intended to be used; and (c) health, safety and environmental benefits and social and economic impact."*

Before making a final registration decision on (S)-methoprene, the PMRA will consider any comments received from the public in response to this consultation document[3]. The PMRA will then publish a Registration Decision[4] on (S)-methoprene, which will include the decision, the reasons for it, a summary of comments received on the proposed final registration decision and the PMRA's response to these comments.

For more details on the information presented in this Overview, please refer to the Science Evaluation of this consultation document.

## What Is (S)-Methoprene?

(S)-methoprene is a mimic of the natural insect juvenile hormone which prevents fly eggs deposited in fresh cattle manure from developing into adult flies. Altosid Beef 2% MUP is used to formulate Altosid Beef Cattle Mineral (0.01% (S)-methoprene), a feed-through product for use to prevent adult horn fly emergence from manure of treated cattle. When (S)-methoprene is included as a component in animal feeds, a significant percentage of the total dose passes through the animal and is present in the manure deposited in field grazing animals. (S)-methoprene is currently registered for use in Canada for control of larval mosquitoes and for control of indoor flea populations in residential settings and on domestic pets.

## Health Considerations

### Can Approved Uses of (S)-Methoprene Affect Human Health?

**Altosid Beef 2% MUP (which is used to formulate Altosid Beef Cattle Mineral), containing (S)-methoprene, is unlikely to affect your health when used according to label directions.**

Potential exposure to (S)-methoprene may occur through the diet (food and water) or when handling and applying products containing (S)-methoprene. When assessing health risks, two key factors are considered: the levels where no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human populations (for example, children and nursing mothers). Only uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

Toxicology studies in laboratory animals describe potential health effects from varying levels of exposure to a chemical and identify the dose where no effects are observed. The health effects noted in animals occur at doses more than 100-times higher (and often much higher) than levels to which humans are normally exposed when pesticide-containing products are used according to label directions.

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3 *"Consultation statement" as required by subsection 28(2) of the Pest Control Products Act.*

4 *"Decision statement" as required by subsection 28(5) of the Pest Control Products Act.*

In laboratory animals, technical grade active ingredient (TGAI) (S)-methoprene was of low acute toxicity via the oral, dermal, and inhalation routes of exposure. It was minimally irritating to the eyes and non-irritating to the skin, and did not produce an allergic skin reaction.

The end-use product, Altosid Beef 2% MUP, which is used to formulate Altosid Beef Cattle Mineral (0.01% (S)-methoprene), is considered to have the same acute toxicity profile as TGAI (S)-methoprene.

Altosid Beef Cattle Mineral was of low acute toxicity via the oral and dermal routes of exposure. It was moderately irritating to the eye, and consequently the signal word and hazard statement "WARNING EYE IRRITANT" are required on the label. It was not irritating to the skin and did not cause an allergic skin reaction.

Registrant-supplied short term and long term (lifetime) animal toxicity tests, as well as information from the published scientific literature were assessed for the potential of (S)-methoprene to cause neurotoxicity, immunotoxicity, chronic toxicity, cancer, reproductive and developmental toxicity, and various other effects. The most sensitive endpoints used for risk assessment included effects on the liver and kidney. There was no indication that the young were more sensitive than the adult animal. The risk assessment protects against these and any other potential effects by ensuring that the level of exposure to humans is well below the lowest dose at which these effects occurred in animal tests.

**Residues in Water and Food**

**Dietary risks from food and drinking water are not of health concern.**

The aggregate dietary intake estimate (food and drinking water) was not conducted since there is no expectation of (S)-methoprene in drinking water as the current use is for a mineral feed supplement for grazing beef cattle. Dietary intake estimates (food alone) revealed that the general population and all subpopulations are expected to be exposed to less than 1% of the acceptable daily intake. Based on these estimates, the chronic dietary risk from (S)-methoprene is not of health concern for all population subgroups.

(S)-Methoprene is not carcinogenic; therefore, a cancer dietary risk assessment is not required.

Animal studies revealed no acute health effects. Consequently, a single dose of (S)-methoprene is not likely to cause acute health effects in the general population (including infants and children).

The *Food and Drugs Act* prohibits the sale of adulterated food, that is, food containing a pesticide residue that exceeds the established maximum residue limit (MRL). Pesticide MRLs are established for *Food and Drugs Act* purposes through the evaluation of scientific data under the *Pest Control Products Act*. Food containing a pesticide residue that does not exceed the established MRL does not pose an unacceptable health risk.

Ruminant feeding studies using (RS)-methoprene were acceptable. The MRLs for this active ingredient can be found in the Science Evaluation section of this consultation document.

**Occupational Health Risks From Handling Altosid Beef 2% MUP**

**Occupational risks are not of concern when Altosid Beef 2% MUP is used according to the proposed label directions, which include protective measures.**

Chemical handlers, feed mill workers and ranchers who mix, load or apply Altosid Beef 2% MUP, which is used to formulate Altosid Beef Cattle Mineral, can come in direct contact with (S)-methoprene residues on the skin. Taking into consideration the label statements, the number of applications and the expectation of the exposure period for handlers and workers, the health risk from exposure to (S)-methoprene for these individuals is not a concern.

## Environmental Considerations

**What Happens When (S)-Methoprene Is Introduced Into the Environment?**

(S)-methoprene is not expected to pose an unacceptable risk to the environment when used according to label directions for the manufacturing of Altosid Beef Cattle, cattle feed.

(S)-methoprene is not expected to pose an unacceptable risk to non-target terrestrial and aquatic species from use in the manufacturing of cattle feed. This is based on the expected limited environmental exposure from the manufacturing process.

## Value Considerations

**What Is the Value of Altosid Beef 2% MUP?**

Altosid Beef 2% MUP, which is used to formulate Altosid Beef Cattle Mineral (0.01% (S)-methoprene), has value as Altosid Beef Cattle Mineral prevents the emergence of adult horn flies from eggs laid in fresh manure from cattle that have consumed this product. Horn flies are the most economically damaging external parasite of cattle and cause injury to cattle by irritation, annoyance, sores (leading to secondary infection), blood loss and stress.

## Measures to Minimize Risk

Labels of registered pesticide products include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions must be followed by law. The PMRA is proposing further risk-reduction measures for product labels.

The key risk-reduction measures being proposed on the label of the end-use product Altosid Beef 2% MUP to address the potential risks identified in this assessment are as follows.

**Key Risk-Reduction Measures**

**Environment**

Additional label statements to protect non-target aquatic organisms will be required.

## Next Steps

Before making a final registration decision on (S)-methoprene, the PMRA will consider any comments received from the public in response to this consultation document. The PMRA will accept written comments on this proposal up to 45 days from the date of publication of this document. Please note that, to comply with Canada's international trade obligations, consultation on the proposed MRLs will also be conducted internationally via a notification to the World Trade Organization. Please forward all comments to Publications (contact information on the cover page of this document). The PMRA will then publish a Registration Decision, which will include its decision, the reasons for it, a summary of comments received on the proposed final decision and the Agency's response to these comments.

## Other Information

When the PMRA makes its registration decision, it will publish a Registration Decision on (S)-methoprene (based on the Science Evaluation of this consultation document). In addition, the test data referenced in this consultation document will be available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa).

# Science Evaluation

## (S)-Methoprene

## 1.0 The Active Ingredient, Its Properties and Uses

### 1.1 Identity of the Active Ingredient

| | |
|---|---|
| **Active substance** | (S)-methoprene |
| **Function** | Insect Growth Regulator |
| **Chemical name** | |
| 1. **International Union of Pure and Applied Chemistry (IUPAC)** | isopropyl (2E,4E,7S)-11-methoxy-3,7,11-trimethyldodeca-2,4-dienoate |
| 2. **Chemical Abstracts Service (CAS)** | 1-methylethyl (2E,4E,7S)-11-methoxy-3,7,11-trimethyl-2,4-dodecadienoate |
| **CAS number** | 65733-16-6 |
| **Molecular formula** | $C_{19}H_{34}O_3$ |
| **Molecular weight** | 310.5 |
| **Structural formula** | |
| **Purity of the active ingredient** | 97.67% |

### 1.2 Physical and Chemical Properties of the Active Ingredient, Manufacturing Concentrate, and End-Use Product

**Technical Product—Precor Insect Growth Regulator**

| Property | Result |
|---|---|
| Colour and physical state | Pale yellow |
| Odour | Faint fruity odour |
| Melting range | N/A |
| Boiling point or range | 270.9°C |
| Specific gravity | 0.911 |
| Vapour pressure at 20°C | 0.623 mPa at 20°C |

| | |
|---|---|
| Ultraviolet (UV)-visible spectrum | $\lambda_{max}$ = 265 nm |
| Solubility in water at 20°C | 6.85 mg/L |
| Solubility in organic solvents at 20°C | Miscible with all common organic solvents.<br>Soluble in most organic solvents, e.g.<br>acetone and hexane > 500 g/L<br>methanol > 450 g/L |
| n-Octanol-water partition coefficient ($K_{ow}$) | log $K_{ow}$ = 6 |
| Dissociation constant ($pK_a$) | N/A |
| Stability (temperature, metal) | Stable in water, organic solvents and in presence of aqueous acids and alkalis. Sensitive to UV light. |

**5 and 6 oz Product — Altosid Beef 2% WR P**

| Property | Altosid Beef 2% WR P |
|---|---|
| Colour | Reddish brown |
| Odour | Molasses-like odour |
| Physical state | Solid |
| Formulation type | Granular |
| Guarantee | 2% |
| Container material and description | Laminate plastic bag with a cable wrap closure |
| Density | 1.33 g/cm$^3$ at 20°C |
| pH of 1% dispersion in water | N/A |
| Oxidizing or reducing action | N/A |
| Storage stability | Stable when stored for one year at warehouse temperature ranging from 5°C to 30°C in commercial packaging. |
| Corrosion characteristics | No evidence of product corrosion to the package was found over two years storage at ambient temperature (5°C to 30°C). |
| Explosibility | Not expected to be explosive. |

### 1.3 Directions for Use

Altosid Beef Cattle Mineral will provide sufficient (S)-methoprene insect growth regulator to prevent the emergence of adult horn flies from manure of treated cattle. Existing adult horn flies will not be affected. Introduction of this product after adult horn fly infestation is established will require treatment of cattle with adulticides if elimination of the adult fly population is desired. Start feeding before horn flies appear and continue use until cold weather marks the end of the horn fly season. Allow free-feeding choice to cattle. Cattle should consume an average of 12.5 g

of Altosid Beef Cattle Mineral per 50 kg of body weight per day, which is equivalent to 0.57 g per day for a 500 kg animal. Locate Altosid Beef Cattle Mineral where cattle congregate (watering, loafing, shade areas) and replenish Altosid Beef Cattle Mineral on a regular basis as needed. If intake of Altosid Beef Cattle Mineral is higher or lower than 0.5–2 g per 50 kg animal body weight per day, the number and placement of feeding locations should be changed as appropriate.

### 1.6 Mode of Action

Altosid Beef Cattle Mineral (0.03% (S)-methoprene) is a feed-through product which is used to prevent adult horn fly emergence from the manure of treated cattle. A sufficient percentage of the total dose passes through the animal and is present in the manure deposited by fed grazing animals to provide control of horn flies. (S)-methoprene, as a mimic of the natural insect juvenile hormone, acts to prevent emergence of adult flies from manure.

## 2.0 Methods of Analysis

### 2.1 Methods for Analysis of the Active Ingredient

The methods provided for the analysis of the active ingredient and impurities in the technical product have been validated and assessed to be acceptable for the determinations.

### 2.2 Method for Formulation Analysis

The method provided for the analysis of the active ingredient in the formulation have been validated and assessed to be acceptable for use as an enforcement analytical method.

### 2.3 Methods for Residue Analysis

A gas chromatographic method with flame ionization detection (GC-FID, Method 0138 in animal matrices) was proposed for enforcement purposes. The method fulfilled the requirements with regards to specificity, accuracy and precision at the method limit of quantitation (LOQ) (0.01 ppm). Acceptable recoveries (70–120%) were obtained in animal matrices. The proposed enforcement method analyses for (RS)-methoprene. Since it has been in the public domain for many years, it is considered to be validated by independent laboratories.

## 3.0 Impact on Human and Animal Health

### 3.1 Toxicology Summary

(S)-methoprene is an insect growth regulator that acts by preventing insect development to the adult stage.

A detailed review of the toxicological database for (S)-methoprene was conducted. The database for (S)-methoprene consists of studies performed both with (S)-methoprene (toxicokinetics, genotoxicity and acute toxicity studies) and the racemic (RS) mixture of methoprene.

(toxicokinetics, genotoxicity, acute and repeated-dose toxicity, oncogenicity, developmental toxicity, and reproductive function studies). Collectively, the data allow for hazard characterization of (S)-methoprene. Many of the studies were performed prior to the widespread use of Good Laboratory Practices (GLP) and/or were considered supplemental due to limitations in study protocol and reporting. In addition, the database is lacking a guideline study assessing reproductive toxicity. The purity of the test material used in the studies was variable. In order to facilitate comparison of the dose levels and effects across studies in the database, the doses were adjusted accordingly when the purity in a study was less than 70%.

Despite the above-noted limitations, the database was considered adequate to define the majority of toxic effects that may result from exposure to (S)-methoprene. Overall, the data suggested a relatively low level of toxicity and NOAELs/LOAELs could be established in the majority of the studies.

Toxicokinetic data for (RS)- and (S)-methoprene were only available following single oral dose administration of radiolabelled material and indicated that both chemicals were relatively rapidly absorbed in mice and guinea pigs, with slower and less extensive absorption in rats. In rats, (RS)-methoprene was metabolized rapidly into endogenous products that were incorporated into body tissues. Peak plasma levels were reached after 6 hours, and the highest concentrations of radioactivity were located in the liver, kidneys, gastrointestinal tract and body fat. At least 12 unidentified metabolites were detected in the urine of rats, along with two major unidentified metabolites in the feces. Only a small fraction of the administered dose was excreted as unchanged parent compound in the feces. A large proportion of radioactivity was excreted in expired air and in the bile, with lesser amounts excreted in the urine and feces. The available data did not indicate any apparent differences in the toxicokinetic profile between the sexes. In a guinea pig study that used only one animal, the majority of the recovered radiolabel consisted of glucuronic acid conjugates and other polar compounds. Parent material comprised the majority of the recovered radioactivity in the feces.

TGAI (S)-methoprene was of low acute toxicity in rats via the oral and inhalation routes of exposure, and was of low acute toxicity in rabbits via the dermal route. It was minimally irritating to the eyes and non-irritating to the skin of rabbits and was not a dermal sensitizer in guinea pigs based on the results of a modified Buehler test. The end-use product Altosid Beef 2% MUP, which is used to formulate Altosid Beef Cattle Mineral (0.01% (S)-methoprene), is considered to have the same acute toxicity profile as TGAI (S)-methoprene.

Altosid Beef Cattle Mineral was of low acute toxicity in rats and rabbits via the oral and dermal routes of exposure, respectively. It was moderately irritating to the eye, but not irritating to the skin of rabbits. It did not produce a dermal sensitization reaction in guinea pigs when tested via the Buehler method.

Several plant and/or animal metabolites were of low acute oral toxicity in rats.

Repeat-dose dietary toxicity studies conducted with (RS)-methoprene in rats, mice and dogs revealed minimal toxicity, with the main findings consisting of increased liver and/or kidney weight, occasionally accompanied by histopathological changes. In the 90-day dietary study in

rats, there was an increased incidence in renal tubular regeneration in males, with increased liver (both sexes) and kidney (males) weights also observed at the next highest dose level. There were no effects in dogs that were considered to be adverse following 90-day dietary administration; increased liver weights and alkaline phosphatase levels were considered adaptive effects at the highest dose tested.

In a supplemental 30-day dermal toxicity study in rabbits with (RS)-methoprene, reduced body-weight gain, body-weight loss, increased leukocyte and neutrophil counts, and increased kidney weight were observed at all dose levels tested. Dermal irritation was observed at the application site of mid- and high-dose animals only. The treated sites were not washed between applications, resulting in a build-up of the test material which con ined with flakes of keratinized skin, hair and dust to form a crust around the application site. Scratching of the affected area, most pronounced in animals of the highest dose group, resulted in skin fissures and injury.

In the 18-month dietary oncogenicity study in mice, histopathological alterations in the liver (brown pigment, focal accumulation of macrophages, small necrotic foci and mononuclear inflammatory cells) were observed at the highest dose tested. There was no evidence of oncogenicity in this study. In the two-year dietary study in rats, adverse findings were limited to the highest dose and consisted of an increased incidence of hepatic lesions in males. No increase in tumours was observed at this dose. The lack of histopathological examination at the lower dose levels precluded the determination of a NOAEL for the study. Despite the limitations in the database, there did not appear to be increased toxicity with increased duration of dosing.

Results of a battery of genotoxicity studies, including an in vivo mouse micronucleus study, did not suggest genotoxic potential.

In oral gavage developmental toxicity studies in mice and rabbits with (RS)-methoprene, no adverse effects on fetal development were observed. In rabbits, abortions, as well as a marked decrease in maternal body-weight gain, were observed at the highest dose tested, which was considered to be well in excess of the limit dose of testing. The mouse study included an additional subgroup of animals that were allowed to deliver their young and rear them for up to 7 weeks. During this time the offspring were examined for developmental parameters and body-weights were recorded. No adverse findings were noted in maternal animals, offspring, or fetuses. The results of these studies provided no evidence of treatment-related malformations and did not suggest that the young animal was more sensitive to toxicity than the adult animal.

A guideline reproductive toxicity study was not available in the database. A non-guideline dietary three-generation study in rats with (RS)-methoprene did not reveal any effects on the ability of the animals to reproduce. Decreases in pup-weight and parental body-weight gain were observed. However, due to limitations in the study protocol, notably the lack of necropsies in all but the F3 pups and the fact that reproductive organs were not examined, the study was considered supplemental and NOAELs were not established.

There was no indication of an effect on the nervous, endocrine or immune systems in the supporting toxicology database or the published literature.

In view of the lack of an adequate study assessing reproductive toxicity, as well as the overall limitations in the toxicology database, a database uncertainty factor of threefold was applied in the risk assessment.

Results of the toxicology studies conducted on laboratory animals in support of (S)-methoprene and its associated end-use products are summarized in Table 2 of Appendix I. The toxicology endpoints for use in the human health risk assessment are summarized in Table 3 of Appendix I.

**Incident Reports**

Since 26 April 2007, registrants have been required by law to report incidents to the PMRA, including adverse effects to health and the environment. Information on the reporting of incidents can be found on the Pesticides and Pest Management portion of the Health Canada website. As of 27 November 2014, a total of 142 human incident reports (involving 157 people in total), and 2848 domestic animal incident reports (involving 3658 animals) have been reported to the PMRA.

Nearly all of the human incidents involved products that contain more than one active ingredient, making it difficult to determine whether (S)-methoprene could have been solely responsible for the reported effects, whereas nearly all of the domestic animal incidents occurred after the animal had been treated directly via the dermal route with a flea and tick control product. A full evaluation of spot-on flea and tick control products is currently being conducted.

Although these incidents involved products that contain (S)-methoprene, none of the products reported in the incidents are considered to be similar to the proposed products that are to be used as a feed-through in cattle.

### 3.1.1 *Pest Control Products Act* Hazard Characterization

For assessing risks from potential residues in food or from products used in or around homes orschools, the *Pest Control Products Act* requires the application of an additional 10-fold factor to threshold effects to take into account completeness of the data with respect to the exposure of, and toxicity to, infants and children, and potential prenatal and postnatal toxicity. A different factor may be determined to be appropriate on the basis of reliable scientific data.

With respect to the completeness of the toxicity database as it pertains to the toxicity to infants and children, the supporting database for (S)-methoprene contained developmental toxicity studies in mice and rabbits; however, a guideline reproductive toxicity study was lacking. A supplemental three-generation study in rats was limited to assessing the ability of the animals to reproduce.

With respect to potential prenatal and postnatal toxicity, there was no indication of increased susceptibility of the young compared to parental animals in the available reproductive and developmental toxicity studies. In the oral gavage developmental toxicity study in mice, in which a subset of maternal animals was allowed to deliver and rear their young for 7 weeks, there were no adverse findings observed in fetuses or offspring. Abortions were observed in the oral gavage rabbit developmental toxicity study. Concern for this serious endpoint was tempered by the fact that the abortions occurred at an excessively high dose level which also resulted in a marked decrease in body-weight gain in the maternal animals.

In view of the above, as well as the fact that concern regarding the lack of an adequate reproductive toxicity study has been addressed through the application of a database uncertainty factor ($UF_{DB}$) of threefold in the risk assessment, the *Pest Control Products Act* factor was reduced to onefold.

### 3.2 Acute Reference Dose (ARfD)

Establishment of an acute reference dose is not required as there were no effects in the toxicology database which were attributable to an acute exposure.

### 3.3 Acceptable Daily Intake (ADI)

To estimate risk from repeated dietary exposure, the 90-day rat dietary study with a NOAEL of 17 mg/kg bw/day was selected for risk assessment. This represented the lowest NOAEL in the database and was based on an increased incidence of renal tubular regeneration observed in males at the LOAEL of 35 mg/kg bw/day. In selecting the appropriate study for establishment of the ADI, consideration was given to other longer-term studies in the toxicology database. The two-year dietary study in rats was not selected as it did not include a complete histopathological examination at all dose levels, and subsequently a NOAEL was not established. In addition, the LOAEL in the 90-day rat study was lower than the NOAEL from the 18-month dietary study in mice (150 mg/kg bw/day), which was based on liver findings. Notwithstanding the limitations in the overall database, there was no apparent increase in toxicity with increased duration of dosing. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied to the NOAEL of 17 mg/kg bw/day from the 90-day rat study. An additional database uncertainty factor of threefold was applied to account for the lack of an adequate reproduction study as well as the overall limitations of studies in the supporting toxicology database. As discussed in the *Pest Control Products Act* Hazard Characterization section, the *Pest Control Products Act* factor was reduced to one fold. **The composite assessment factor (CAF) is therefore 300.**

The ADI is calculated according to the following formula:

$$\text{ADI} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{17 \text{ mg/kg bw/day}}{300} = 0.06 \text{ mg/kg bw/day of (S)-methoprene}$$

**Cancer Assessment**

There was no evidence of carcinogenicity and therefore, a cancer risk assessment was not necessary.

## 3.4 Occupational and Residential Risk Assessment

### 3.4.1 Toxicological Endpoints

**Short- and Intermediate-Term Dermal and Inhalation**

Occupational exposure is characterized as intermediate-term in duration for feed mill workers and ranchers and to occur by the dermal and inhalation routes.

For short- and intermediate-term dermal and inhalation risk assessments, the NOAEL of 17 mg/kg bw/day from the 90-day dietary study in rats was selected. The NOAEL was based on an increased incidence of renal tubular regeneration observed in males at the LOAEL of 35 mg/kg bw/day. The available short-term dermal toxicity in rabbits was considered supplemental due issues related to study design and conduct, and therefore was not appropriate for use in endpoint selection. An acceptable repeat-dose inhalation study was not available.

The target Margin of Exposure (MOE) for these scenarios is 300, which includes uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability as well as an additional uncertainty factor of threefold to account for the lack of an adequate reproductive toxicity study as well as overall limitations of studies in the supporting database. The selection of this study and MOE is considered to be protective of all populations, including nursing infants and the unborn children of exposed female workers.

### 3.4.2 Occupational Exposure and Risk

#### 3.4.2.1 Chemical Handler and Feed Mill Worker Exposure and Risk Assessment

Individuals have potential for exposure to (S)-methoprene during mixing and loading of Altosid Beef 2% MUP and during bagging, sewing and stacking in a feed mill. Dermal and inhalation exposure estimates for chemical handlers and feed mill workers were generated from the Pesticide Handlers Exposure Database (PHED).

Exposure to chemical handlers mixing and loading Altosid Beef 2% MUP and to workers bagging, sewing and stacking the formulated product is expected to be intermediate-term in duration and to occur primarily by the dermal and inhalation routes. Exposure estimates were derived for manually mixing and loading Altosid Beef 2% MUP to the batch mixer and for workers bagging, sewing and stacking the formulated product in the feed mill. The exposure estimates are based on workers wearing a long-sleeved shirt, long pants and no gloves.

As chemical-specific data for assessing human exposures were not submitted, dermal and inhalation exposures for workers mixing and loading were estimated using the PHED Version 1.1. PHED is a compilation of generic mixer/loader and applicator passive dosimetry data with associated software, which facilitates the generation of scenario-specific exposure estimates.

Dermal exposure was estimated by coupling the unit exposure values (Table 3.4.2.1.1) with the amount of product handled per day and 100% dermal absorption. Inhalation exposure was estimated by coupling the unit exposure values with the amount of product handled per day and 100% inhalation absorption. Exposure was normalized to mg/kg bw/day by using an 80 kg adult body weight.

Exposure estimates were compared to the toxicological endpoints (NOAEL, no observed adverse effects levels) to obtain the margin of exposure (MOE); the target MOE is 300. The MOEs for chemical handlers and baggers, sewers and stackers were above the target for dermal and inhalation exposure, and therefore, occupational health risk associated with handling Altosid Beef 2% MUP and the formulated product is not of concern. The exposure and risk estimates are presented in Table 3.4.2.1.2.

**Table 3.4.2.1.1 PHED unit exposure estimates for handling Altosid Beef 2% MUP**

| Scenario | | Dermal | Inhalation [a] | Total unit exposure |
|---|---|---|---|---|
| **Mixer/loader PHED estimates (single layer, no gloves[b])** | | | | |
| A | Open pour mixing/loading a dry flowable | 163.77 | 1.02 | 164.79 |

[a] Light inhalation rate

[b] Single layer, glove data was used as it is a higher unit exposure and has greater data confidence versus single layer, no glove data.

**Table 3.4.2.1.2 Chemical handler and bagger, sewer and stacker risk assessment for workers wearing a single layer and no gloves**

| Exposure scenario | Unit exposure (µg/kg a.i. handled) | Amount handled (kg/day) | Exposure (mg/kg bw/day) [a] | MOE [b] |
|---|---|---|---|---|
| **Open M/L, PPE: Single layer and no gloves** | | | | |
| Mixer/loader | 164.79 | 2.724 | 0.00561 | 3,030 |
| Bagger/sewer/stacker | 164.79 | 2.724 | 0.00561 | 3,030 |

[a] Exposure = (Unit exposure x Amount handled) / (80 kg bw x 1000 µg/mg)

[b] Dermal and inhalation NOAEL = 17 mg/kg bw/day; target MOE = 300

### 3.4.2.2 Rancher Exposure and Risk Assessment

Ranchers have potential for exposure to (S)-methoprene during opening and pouring of the formulated product, Altosid Beef Cattle Mineral, into cattle feeding troughs. Dermal and inhalation exposure estimates for ranchers were generated from the Pesticide Handlers Exposure Database (PHED).

Exposure to ranchers handling Altosid Beef Cattle Mineral is expected to be intermediate-term in duration and to occur primarily by the dermal and inhalation routes. Exposure estimates were derived for manually opening and pouring bags of Altosid Beef Cattle Mineral in feeding troughs in the pasture. The exposure estimates are based on ranchers wearing a long-sleeved shirt, long pants and no gloves.

As chemical-specific data for assessing human exposures were not submitted, dermal and inhalation exposures for workers mixing and loading were estimated using the PHED. Version 1.1. PHED is a compilation of generic mixer/loader and applicator passive dosimetry data with associated software which facilitates the generation of scenario-specific exposure estimates.

Dermal exposure was estimated by coupling the unit exposure values with the amount of product handled per day and 100% dermal absorption. Inhalation exposure was estimated by coupling the unit exposure values with the amount of product handled per day and 100% inhalation absorption. Exposure was normalized to mg/kg bw/day by using an 80 kg adult body-weight.

Exposure estimates were compared to the toxicological endpoints (NOAEL) to obtain the MOE; the target MOE is 300. The MOE for ranchers was above the target for dermal and inhalation exposure, and therefore, occupational health risk associated with handling the formulated feed product, Altosid Beef Cattle Mineral, is not of concern. The exposure and risk estimates are presented in Table 3.4.2.2.1.

**Table 3.4.2.2.1 Rancher risk assessment for workers wearing a single layer and no gloves**

| Exposure scenario | Unit exposure (µg/kg a.i. handled) | Amount handled (kg/day) | Exposure (mg/kg bw/day) [a] | MOE [b] |
|---|---|---|---|---|
| **Open M/L, PPE: Single layer and no gloves** | | | | |
| Rancher | 164.79 | 0.0908 | 0.000187 | 90,900 |

[a] Exposure = (Unit exposure x Amount handled) / (80 kg bw x 1000 µg/mg)
[b] Dermal and inhalation NOAEL = 17 mg/kg bw/day; target MOE = 300

### 3.4.2.3 Exposure Assessment for Ranchers in the Pasture Following Product Use

(S)-methoprene residues are expected to be a component of the manure at efficacious concentrations to control horn flies. It was assumed that manure containing (S)-methoprene may be removed from areas where cattle congregate and that feed troughs may be cleaned on occasion. However, these practices were not expected to be typical duties for a rancher. In addition, potential exposure for ranchers removing manure using farm tools and for cleaning feed

troughs was expected to be much less than for handling the product and was considered negligible. As such, no postapplication exposure is anticipated following addition of the formulated feed product, Altosid Beef Cattle Mineral, in the pasture and no further assessment was required.

### 3.4.3 Residential Exposure and Risk Assessment

#### 3.4.3.1 Handler Exposure and Risk

Altosid Beef 2% MUP is not a domestic product; therefore, a residential handler assessment was not required.

## 3.5 Food Residues Exposure Assessment

### 3.5.1 Residues in Animals

The residue definition for risk assessment and enforcement in all ruminant commodities is (RS)-methoprene. The enforcement analytical method is valid for the quantitation of methoprene residues in livestock matrices. An adequate feeding study was carried out to assess the anticipated residues in cattle matrices that would result from the use of Altosid Beef Cattle Mineral supplement containing (S)-methoprene. The feeding study is sufficient to support the proposed maximum residue limits.

### 3.5.2 Dietary Risk Assessment

Chronic non-cancer dietary risk assessment was conducted using the Dietary Exposure Evaluation Model (DEEM–FCID™), which incorporates food consumption data from the National Health and Nutritional Examination Survey, *What We Eat in America*, (NHANES/WWEIA) a dietary survey available through CDC's National Centre for Health Statistics.

#### 3.5.2.1 Chronic Dietary Exposure Results and Characterization

The Canadian MRLs were applied to the basic chronic non-cancer analysis for (S)-methoprene. The basic chronic dietary exposure from all supported (S)-methoprene food uses (alone) for the total population, including infants and children, and all representative population subgroups is less than 1% of the acceptable daily intake (ADI). Aggregate exposure from food and drinking water was not considered, since exposure from drinking water is not expected as the current use is for a mineral feed supplement for grazing beef cattle.

#### 3.5.2.2 Acute Dietary Exposure Results and Characterization

No attributable acute health effects were established from the animal toxicity studies. Consequently, a single dose was not identified as it is not likely to cause acute health effects for the general population (including children and infants).

### 3.5.3 Aggregate Exposure and Risk

There is no aggregate risk to (S)-methoprene as exposure consists of food only, as residues in drinking water sources are not expected and there are no residential uses.

### 3.5.4 Maximum Residue Limits

**Table 3.5.4.1 Proposed Maximum Residue Limits**

| Commodity | Recommended MRL (ppm) |
|---|---|
| Fat of cattle | 0.1 |
| Meat of cattle | 0.01 |
| Meat byproducts of cattle | 0.02 |

The nature of the residues in animal matrices, analytical methodologies, feeding studies, and chronic dietary risk estimates are summarized in Tables 1, 4 and 5 in Appendix I.

## 4.0 Impact on the Environment

### 4.1 Fate and Behaviour in the Environment

For more information on the fate and behaviour in the environment of Precor Insect Growth Regulator containing (S)-Methoprene, please see PACR2007-01[5].

### 4.2 Environmental Risk Characterization

A qualitative risk assessment was conducted for the proposed use as a manufacturing concentrate for cattle feed. The exposure of non-target organisms in the environment to (S)-Methoprene is expected to be limited. (S)-Methoprene is considered to be non-persistent in terrestrial and aquatic environments (see PACR 2007-10). The PMRA therefore concludes that the use of Precor Insect Growth Regulator (containing (S)-Methoprene) as manufacturing concentrate for cattle feed is not expected to pose a risk to terrestrial or aquatic non-target organisms.

## 5.0 Value

### 5.1 Consideration of Benefits

Altosid Beef 2% MUP, which is used to formulate Altosid Beef Cattle Mineral (0.01% (S)-methoprene), has value as Altosid Beef Cattle Mineral prevents the emergence of adult horn flies from eggs laid in fresh manure from cattle which have consumed this product. The horn fly (*Haematobia irritans*) is North America's most pervasive external cattle parasite and the most

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[5] *PACR2007-01, Proposed Acceptability for Continuing Registration 2007-01: Re-evaluation of S-methoprene*

economically damaging to the cattle industry. Horn flies are blood feeders, staying on the sides and bellies of infested animals day and night. Horn flies leave the animals to lay eggs in freshly deposited manure, where the larvae grow and develop until emergence as adults.

Horn flies cause irritation and annoyance to herds, sores (leading to secondary infection), blood loss and stress. This can lead to economic damage to infested herds by reduced grazing time, increased energy consumption, decreased feeding efficiency, lower milk production, decreased weight gain, lower body condition, and lower conception rates.

While several sprays, dusts, pour-on products, and ear tags are registered to control adult horn fly on cattle, there are no feed-through products registered for this use in Canada. Altosid Beef 2% MUP, when used to formulate Altosid Beef Cattle Mineral, has value as it is both compatible with current adult horn fly pest control, cattle production methods, and it provides end-users with a new method of controlling this pest during the larval stage and before it is a concern for the cattle. In addition, unlike many conventional chemical control products, resistance to (S)-methoprene is not expected as it is a mimic of juvenile growth hormone. Juvenile growth hormone is naturally produced by insects and is required for development during the juvenile stages. Therefore, Altosid Beef 2% MUP, when used to formulate Altosid Beef Cattle Mineral, has value as a sustainable control product for horn fly in cattle.

### 5.2 Acceptable Claims and Effectiveness Against Pests

One laboratory bioassay trial using field-collected manure from cattle treated with (S)-methoprene using 0.01% (S)-methoprene mineral blocks was reviewed in support of the control claims for Altosid Beef 2% MUP when used to formulate Altosid Beef Cattle Mineral. The results of the laboratory bioassay showed 99% inhibition of horn fly development. This study demonstrated that when a feed-through mineral supplement formulated with 0.01% (S)-methoprene is fed to beef cattle, the development of horn fly in manure is inhibited. In addition to the submitted study, the long history of use of (S)-methoprene in the United States, where it has been registered as a feed-through product in beef cattle to control horn fly for over 30 years, was cited in support of this use. Based on the study results and history of use, it is expected that Altosid Beef 2% MUP, when used to formulate Altosid Beef Cattle Mineral, will prevent adult horn fly emergence from the manure of treated cattle.

### 5.3 Non-Safety Adverse Effects

No non-safety adverse effects are expected from use of Altosid Beef 2% MUP when used to formulate Altosid Beef Cattle Mineral.

### 5.4 Supported Uses

Based on the reviewed value information, the use of Altosid Beef 2% MUP to formulate Altosid Beef Cattle Mineral at an application rate of 12.5 g product per 50 kg of body-weight per day, applied using free-feeding to cattle, is supported to prevent the emergence of horn fly adults from the manure of treated cattle.

## 6.0 Pest Control Product Policy Considerations

### 6.1 Toxic Substances Management Policy Considerations

The Toxic Substances Management Policy (TSMP) is a federal government policy developed to provide direction on the management of substances of concern that are released into the environment. The TSMP calls for the virtual elimination of Track 1 substances [those that meet all four criteria outlined in the policy, for example, persistent (in air, soil, water and/or sediment), bio-accumulative, primarily a result of human activity and toxic as defined by the Canadian Environmental Protection Act].

During the review process, (S)-methoprene and its transformation products were assessed in accordance with the PMRA Regulatory Directive DIR99-03[6] and evaluated against the Track 1 criteria. The PMRA has reached the following conclusions:

- (S)-methoprene does not meet Track 1 criteria, and is not considered a Track 1 substance.
- (S)-methoprene is not expected to bio-accumulate in the environment.

### 6.2 Formulants and Contaminants of Health or Environmental Concern

During the review process, contaminants in the technical and formulants and contaminants in the end-use products are compared against the *List of Pest control Product Formulants and Contaminants of Health or Environmental Concern* maintained in the *Canada Gazette*[7]. The list is used as described in the PMRA Notice of Intent NOI2005-01[8] and is based on existing policies and regulations including: DIR99-03; and DIR2006-02[9], and taking into consideration the Ozone-depleting Substance Regulations, 1998, of the *Canadian Environmental Protection Act* (substances designated under the Montreal Protocol). The PMRA has reached the following conclusions:

- Technical grade active ingredient (S)-methorpene (Precor Insect Growth Regulator), and the end-use product (Altosid Beef 2% MUP) do not contain any formulants or contaminants of health or environmental concern identified in the *Canada Gazette*.

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6 *DIR99-03, The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy.*

7 *Canada Gazette, Part II, Volume 139, Number 24, SI/2005-114 (2005-11-30) pages 2641 -2643: List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern, and to the order amending this list in the Canada Gazette, Part II, Volume 142, Number 13, SI/2008-47 (2008-06-25) pages 1611-1613. Part 1 Formulants of Health or Environmental Concern, Part 2 Formulants of Health or Environmental Concern that are Allergens Known to Cause Anaphylactic-Type Reactions and Part 3 Contaminants of Health or Environmental Concern.*

8 *NOI2005-01, List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern under the New Pest Control Products Act.*

9 *DIR2006-02, PMRA Formulants Policy.*

The use of formulants in registered pest control products is assessed on an ongoing basis through PMRA formulant initiatives and Regulatory Directive DIR2006-02.

## 7.0 Summary

### 7.1 Human Health and Safety

The toxicology database submitted for (S)-methoprene is adequate to define the majority of toxic effects that may result from exposure. There was no evidence of carcinogenicity in rats or mice after longer-term dosing, and (S)-methoprene was not considered to be genotoxic. (S)-methoprene was not a developmental toxicant in mice or rabbits. Although information regarding the effects of (S)-methoprene on reproduction were limited, the available data did not indicate adverse effects on the ability of animals to reproduce. There was no evidence of increased susceptibility of the young in the available studies. (S)-methoprene was not neurotoxic. In short-term and chronic studies on laboratory animals, the primary target organs were the liver and kidney. The risk assessment protects against the toxic effects noted above by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

Mixers and loaders handling Altosid Beef 2% MUP and baggers, sewers and stackers and ranchers handling the formulated feed product, Altosid Beef Cattle Mineral, are not expected to be exposed to levels of (S)-methoprene that will result in health risks of concern when Altosid Beef 2% MUP is used according to the label directions.

The nature of the residue in animals is adequately understood. The residue definition for enforcement and risk assessment is (RS)-methoprene in animal matrices. The proposed use of (S)-methoprene as a feed supplement for cattle to control horn flies in manure does not constitute a health risk of concern for chronic dietary exposure (food) to any segment of the population, including infants, children, adults and seniors. Sufficient feeding studies have been reviewed to recommend MRLs. The PMRA recommends that the following MRLs be specified for residues of (RS)-methoprene.

| Commodity | Recommended MRL (ppm) |
|---|---|
| Fat of cattle | 0.1 |
| Meat of cattle | 0.01 |
| Meat byproducts of cattle | 0.02 |

### 7.2 Environmental Risk

The use of Precor Insect Growth Regulator (containing (S)-Methoprene) for use in the manufacturing of Altosid Beef 2% MUP and Altosid Beef Cattle mineral, is not expected to pose a risk to terrestrial or aquatic non-target organisms.

### 7.3 Value

*Altosid Beef 2% MUP, when used to formulate Altosid Beef Cattle Mineral, has value as it prevents the emergence of adult horn flies from eggs laid in fresh manure from cattle which have consumed this product at an application rate of 12.5 g product per 50 kg of body-weight per day. Horn flies are the most economically damaging external parasite of cattle and cause injury to cattle by irritation, annoyance, sores (leading to secondary infection), blood loss and stress. Altosid Beef 2% MUP, when used to formulate Altosid Beef Cattle Mineral, has value as it is compatible with current horn fly pest control and cattle production methods. It also provides end-users with a new method of controlling this pest while they are in the larval stage and before they are a concern for the cattle. It is a sustainable pest control product as horn fly are unlikely to develop resistance to (S)-methoprene.*

## 8.0 Proposed Regulatory Decision

*Health Canada's PMRA, under the authority of the Pest Control Products Act and Regulations, is proposing full registration for the sale and use of Precor Insect Growth Regulator and Altosid Beef 2% MUP. Altosid Beef 2% MUP will be used to manufacture the final product Altosid Beef Cattle Mineral to control horn flies on beef cattle, which is exempt from registration under the Pest Control Products Act in accordance with paragraph 8(1)(b) of the Pest Control Product Regulations, and, more specifically, Schedule 2, Section 1.*

*An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.*

## List of Abbreviations

| | |
|---|---|
| a.i. | *active ingredient* |
| ADI | *administered dose* |
| ADE | *acceptable daily intake* |
| ALS | *acetolactate synthase* |
| ARfD | *acute reference dose* |
| bw | body weight |
| bwg | body-weight gain |
| CAF | *composite assessment factor* |
| CAS | Chemical Abstracts Service |
| cm | centimetres |
| CNS | central nervous system |
| EEC | *estimated environmental concentration* |
| F0 | *initial parent generation* |
| F1 | *first filial generation* |
| F2 | *second filial generation* |
| F3 | *third filial generation* |
| fc | food consumption |
| g | gram |
| GC-FID | *gas chromatographic method with flame ionization detection* |
| GLP | *good laboratory practice* |
| ha | hectare |
| HNOEL | highest *no-observed-effect-level* |
| HDPE | high density polyethylene |
| HDT | highest dose tested |
| HPLC-MS/MS | high performance liquid chromatography with tandem mass spectrometry |
| HNO3 | hour(s) |
| IUPAC | International Union of Pure and Applied Chemistry |
| i.v. | intravenous |
| JMPR | Joint FAO/WHO Meeting on Pesticide Residues |
| kg | kilogram |
| $K_{ow}$ | *n*-octanol-water partition coefficient |
| L | litre |
| $LC_{50}$ | lethal concentration 50% |
| $LD_{50}$ | lethal dose 50% |
| LOAEL | lowest observed adverse effect level |
| LOQ | limit of quantitation |
| LSC | liquid scintillation counting |
| mg | milligram |
| mL | millilitre |
| MTD | maximum tolerated dose |
| MIS | maximum irritation score |
| MRL | maximum residue |
| MMAD | mass median aerodynamic diameter |

| | |
|---|---|
| mPa | millipascal |
| MOE | margin of exposure |
| MRL | maximum residue limit |
| MRM | multiresidue method |
| m/z | mass-to-charge ratio of an ion |
| N/A | not applicable |
| nm | nanometre |
| NAFTA | North American Free Trade Agreement |
| NMR | nuclear magnetic resonance |
| NOAEL | no observed adverse effect level |
| NR | not reported |
| NZW | New Zealand white |
| PHED | Pesticide Handlers Exposure Database |
| pKa | dissociation constant |
| PMRA | Pest Management Regulatory Agency |
| PND | postnatal day |
| PPE | personal protective equipment |
| ppm | parts per million |
| PSD | Pesticides Safety Directorate (UK) |
| RAC | raw agricultural commodity |
| RD | residue definition |
| rel | relative |
| TGAI | technical grade active ingredient |
| TRR | total radioactive residue |
| TSMP | Toxic Substances Management Policy |
| US | United States |
| UV | ultraviolet |
| wt | weight |
| µg | microgram |

# Appendix I Tables and Figures

**Table 1 Residue Analysis**

| Matrix | Method ID | Analytes | Method Type | LOQ | Reference |
|---|---|---|---|---|---|
| Animal | Method #038 | (RS)-Methoprene (racemic mixture) | GC-FID with OV-101 and OV-225 columns or GC MS for confirmation | 0.01 ppm | PMRA # 2194964 |

**Table 2a Toxicity Profile of the Product Altosid Beef Cattle Mineral**

| Study Type/Animal/PMRA # | Study Results |
|---|---|
| Acute Oral $LD_{50}$<br>Standard Test (401)<br><br>Rats<br><br>PMRA#2194949 | $LD_{50}$ ♂♀ > 5050 mg/kg bw<br><br>Low Toxicity |
| Acute Dermal $LD_{50}$<br><br>Rabbits<br><br>PMRA#2194951 | $LD_{50}$ ♂♀ > 5050 mg/kg bw<br><br>Low Toxicity |
| Acute Inhalation $LC_{50}$<br><br>PMRA #2338867, #2375326 | Waiver requested based on the fact that the product is a granule which is not expected to generate a respirable dust. A study demonstrating that the product was resistant to attrition was submitted, in addition to a study which showed that there were no particles which were considered to be of respirable size (less than 5 µm). |
| Primary Eye Irritation<br><br>Rabbit<br>(single rabbit whose eye was not rinsed for 24 hrs)<br><br>PMRA #2194952 | MAS (one rabbit)=26.3/110<br>MIS = 29/110, at 48 hrs<br><br>Moderately Irritating |
| Primary Skin Irritation<br><br>Rabbits<br><br>PMRA #2194953 | MAS=0/8<br>MIS= 0/8<br><br>Non-irritating |
| Skin Sensitization<br>Buehler<br><br>Guinea pigs<br><br>PMRA #2194954 | Negative |

**Table 2b Toxicity Profile of the Manufacturing Use Product Altosid Beef 2% MUP**

| |
|---|
| The manufacturing use product, Altosid Beef 2% MUP, is considered to have the same acute toxicity profile as TGAI (S)-methoprene (see Table 20c) |

**Table 2c Toxicity Profile of Technical (S)-methoprene**

Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons. Organ weight effects reflect both absolute organ weights and relative organ to body-weights, unless otherwise noted. Effects seen above the LOAEL(s) have not been reported in this table for most studies for reasons of brevity.

| Study Type/ Animal/PMRA # | Study Results |
|---|---|
| **Toxicokinetics** | |
| Single oral gavage (RS)-methoprene<br><br>Mouse<br><br>JMPR (2001) | 8 ♂ and 2 pregnant ♀ were dosed in the study.<br><br>Within 24 hr, 64% of administered radiolabel was recovered in urine and 12% in feces. By 96 hr – 68% in urine and 14% in feces (18% unaccounted for). Elimination in expired air was not measured.<br><br>Large amounts of radiolabel were found in the stomach and small amounts in the liver and kidney 0.5 to 2 hrs after administration. Six hours after administration, radiolabel was found primarily in the small intestine, descending colon and rectum. No radiolabel appeared to have been transferred across the placenta 6 or 96 hr after administration. Very little radiolabel was detected in the body at 12 hr. |
| Single oral gavage (RS)-methoprene<br><br>Rat<br>(series of experiments)<br><br>PMRA #2194874, 2194876 | A dose of 25 mg/kg bw/day was used in the study.<br><br>1st experiment (excretion in urine, feces and expired air):<br>Methoprene was slowly and incompletely absorbed and eliminated. Within 24 hr, 26% of the administered radiolabel was excreted in expired air, 13% in urine and 5.2% in feces. After 48 hr excretion was 33% (expired air), 17% (urine) and 12% (feces). After 120 hr approximately 77% of the administered radiolabel was excreted (39% in expired air, 20% in urine and 18% in feces) with 17% remaining in the carcass. There were no apparent differences between the sexes. Excretion appeared to be biphasic, with rapid elimination during the first 24 hr and much slower elimination thereafter. The excretion half-life for approximately 60% of the radioactivity was 10 hr.<br><br>2nd experiment (bile duct-cannulated rats):<br>27% of the administered radiolabel excreted in the bile, 5.9% in urine and 12% in feces within 48 hr. |

| | |
|---|---|
| | At least 12 unidentified metabolites were detected in urine, and two major unidentified metabolites were detected in bile. Unchanged parent was only found in feces as a small fraction of the total excreted radiolabel, and likely represented unabsorbed compound as the bile contained no parent material. Since a large proportion of radiolabel was excreted in expired air, methoprene appears to be extensively metabolized.<br><br>3rd experiment (radioactivity in blood):<br>Plasma concentration of radiolabel peaked after about 6 hr, with total amount of radiolabel corresponding to 1.6% of administered dose, followed by a relatively slow decline with a half-life of about 48 hr.<br><br>4th experiment (radioactivity in tissues):<br>Peak tissue concentrations in well-perfused organs were reached after 6-12 hr. Six hours after administration the highest concentrations were found in the liver (1.7%), kidneys (0.58%) and lungs (0.52%). Concentration in fat peaked at 12 hrs (0.73%). |
| Single oral or i.v. dose (S)-methoprene<br><br>Sprague Dawley rat<br><br>PMRA #2194875 | Following i.v. administration, the concentration of unchanged methoprene in blood declined steadily over the 7 hr period.<br><br>Following oral administration, the concentration of unchanged methoprene in blood peaked after 2 hr (representing approx. 12% of total radiolabel in blood). In fat, the concentration of unchanged methoprene reached a plateau 3-4 hrs after i.v. administration and 4-6 hr after oral administration, and subsequently declined very slowly. Almost all radiolabel in fat represented unchanged methoprene following either i.v. or oral dosing. |

| | |
|---|---|
| Single oral dose<br>(RS)-methoprene<br><br>Guinea pig<br><br>JMPR (2001) | 50% of the radiolabel was excreted within 24 hr (24% in urine, 9% in feces, 17% in expired air). The peak concentration of radiolabel in urine was reached 5.5 hr after dosing.<br><br>At 24 hrs, blood contained 19 mg equivalent per mL, muscle and fat contained 3.3 and 11 mg equivalent per gram wet tissue, respectively.<br><br>95-99% of the recovered radiolabel consisted of glucuronic acid conjugates and other polar compounds. After treatment with glucuronidase, the two main metabolites were identified as 11-methyoxy-3,7,11-trimethyldodcea-2,4-dienoic acid and 11-hydroxy-3,7,11-trimethyldodeca-2,4-dienoic acid, accounting for 75% of the radiolabel in urine. Isopropyl-11-hydroxy-3,7,11-trimethyldodeca-2,4-dienoate and 7-methoxy citronellic acid were also identified. No parent material was detected in urine.<br><br>In feces, 77% of the recovered radiolabel was parent material, with smaller quantities (3-8%) of 11-methyoxy-3,7,11-trimethyldodeca-2,4-dienoic acid, 11-hydroxy-3,7,11-trimethyldodeca-2,4-dienoic acid, and isopropyl-11-hydroxy-3,7,11-trimethyldodeca-2,4-dienoate. |
| **Acute Toxicity Studies- (S)-methoprene** | |
| Acute oral toxicity<br>(S)-methoprene<br><br>Sprague Dawley rat<br><br>PMRA #1233603 | $LD_{50}$ >5000 mg/kg bw<br><br>No mortalities or overt signs of toxicity were observed. Animals gained weight throughout the study. No gross abnormalities upon necropsy.<br><br>**Low toxicity** |
| Acute dermal toxicity<br>(S)-methoprene<br><br>NZW rabbit<br><br>PMRA#1233604 | $LD_{50}$ >2000 mg/kg bw<br><br>No mortalities, overt signs of toxicity or skin irritation observed. No gross abnormalities upon necropsy.<br><br>**Low toxicity** |
| Acute inhalation toxicity<br>(S)-methoprene<br><br>Sprague Dawley rat<br><br>PMRA #1288788 | $LC_{50}$ > 5.19 mg/L<br><br>MMAD = 2.1µm<br>There were no mortalities in the study.<br><br>**Low toxicity** |
| Dermal irritation<br>(S)-methoprene<br><br>NZW rabbit<br><br>PMRA #1233606 | MAS = 0<br>MIS = 0<br><br>No signs of skin irritation or toxicity observed in any animal.<br><br>**Non-irritating** |

| | |
|---|---|
| Eye irritation<br>(S)-methoprene<br><br>NZW rabbit<br><br>PMRA #1233605 | MAS = 0.66<br>MIS = 3.3 at 1 hr<br><br>Slight irritation (score of 1 for erythema and chemosis) was observed in 2♀ and 3 ♂ after 1 hr, but all irritation had subsided by 48-72 hr. No corneal opacity, iritis or abnormal discharge noted in any of the animals.<br><br>**Minimally irritating** |
| Dermal sensitization<br>(S)-methoprene<br>(Modified Buehler)<br><br>Guinea pig<br><br>PMRA #2338850 | **Negative** |
| **Acute toxicity studies – (RS)-methoprene** | |
| Acute oral toxicity<br><br>Sprague Dawley rat<br><br>EPA (1991) | $LD_{50}$ > 10,000 mg/kg bw<br><br>All animals survived. No gross pathologic changes related to treatment observed at necropsy |
| Acute oral toxicity<br><br>Beagle dog<br><br>JMPR (2001) | $LD_{50}$ > 5000 mg/kg bw<br><br>No clinical signs of toxicity or treatment-related pathological changes at necropsy. |
| Acute oral toxicity<br><br>Beagle dog<br><br>JMPR (2001) | $LD_{50}$<10,000 mg/kg bw<br><br>Females died after 30-40 minutes, one male died at 2 hrs and the other male was sacrificed after 3 hrs.<br>Clinical signs of toxicity included dilation of pupils, rapid respiration, convulsions, vomiting, salivation, and ataxia. Gross examination revealed congestion of the kidneys, liver, lungs and scleral vessels. Two animals had signs of cardiac effects. Signs of minor congestion were observed in the CNS, haematopoietic tissues, reproductive and digestive tracts. |
| Acute dermal toxicity<br><br>Rabbit –strain not specified<br><br>PSD (1993) | $LD_{50}$ >3038 mg/kg bw |

| | |
|---|---|
| Eye irritation<br><br>NZW rabbit<br><br>JMPR (2001) | No signs of irritation were observed |
| Eye irritation<br><br>NZW rabbit<br><br>JMPR (2001) | Slight erythema of the conjunctivae was observed in all treated eyes 1 hr after dosing. No signs of irritation were observed 1, 2, 3, or 7 days after dosing. |
| Dermal irritation<br><br>NZW rabbit<br><br>JMPR (2001) | No signs of irritation were observed immediately or 48 hr after removal of the occlusive dressing. |
| Dermal irritation<br><br>NZW rabbit<br><br>JMPR (2001) | Slight erythema observed immediately after removal of the dressing at 4/6 abraded sites and 2/6 intact sites. Barely perceptible erythema observed next to the abrasions at 5/6 sites 48 hr after removal of dressings. |
| Dermal sensitization<br><br>Guinea pig<br>Landsteiner's method<br><br>PMRA #1249492 | Mild, temporary erythema was observed in some animals during the induction phase shortly after the injection of methoprene or the vehicle, but the intensity of the reactions did not increase with repeated administration.<br><br>Negative |

| **Short-term toxicity studies** | |
|---|---|
| 30-day dermal<br>(RS)-methoprene<br><br>Japanese rabbit<br><br>PMRA #1229383 | NOAEL not established<br><br>**Systemic toxicity:**<br>Effects at ≥100 mg/kg bw/day: ↑leukocytes; ↓bw/ bwg, bw loss, ↑neutrophil count, ↑rel. kidney wt (♀)<br><br>Effects at ≥300 mg/kg bw/day: ↑neutrophil count; vocalization after treatment, ↓bw/bwg, bw loss, ↑rel. kidney wt (♂)<br><br>**Dermal irritation:**<br>Effects at ≥100 mg/kg bw/day: thickening of the epidermal prickle-cell layer at the application site<br><br>Effects at ≥300 mg/kg bw/day: erythema at the application site.<br><br>**Supplemental** |
| 28 day oral (diet) tolerance study<br>(RS)-methoprene<br><br>CD-1 mouse<br><br>PMRA #1229388 | NOAEL not established<br><br>Effects at 16000 ppm (2400 mg/kg bw/day): bw loss, slight hypoactivity and hypothermia; mortality (♂); white/yellow foci in the liver (♀)<br><br>**Supplemental** |
| 14 day oral (diet)<br>Range-finding<br>(RS)-methoprene<br><br>Sprague Dawley rat<br><br>JMPR (2001) | NOAEL not established<br><br>Effects at ≥20,000 ppm (1378 mg/kg bw/day; corrected for purity): ↓fc, ↓bw (attributed to poor palatability of the diet)<br><br>**Supplemental** |
| 90 day oral (diet)<br>(RS)-methoprene<br><br>Sprague Dawley rat<br><br>PMRA #1229378 | NOAEL = 500 ppm (17 mg/kg bw/day)<br>LOAEL = 1000 ppm (35 mg/kg bw/day; corrected for purity)<br>Effects at the LOAEL: ↑renal tubular regeneration (♂) |
| 90 day oral (diet)<br>(RS)-methoprene<br><br>Beagle dog<br><br>PMRA #1229378 | NOAEL = 5000 ppm (86 mg/kg bw/day corrected for purity) (HDT)<br>LOAEL not established |

| | |
|---|---|
| **Chronic toxicity/oncogenicity studies** | |
| 18 month oncogenicity<br>(diet)<br>(RS)-methoprene<br><br>CD mouse<br><br>PMRA #1229375 | NOAEL = 1000 ppm (150 mg/kg bw/day)<br>LOAEL = 2500 ppm (380 mg/kg bw/day)<br>Effects at the LOAEL: ↑ brown pigment in the liver of most animals, focal accumulation of macrophages with brownish foamy cytoplasm in the liver, often associated with small necrotic foci and mononuclear inflammatory cells<br><br>**Not oncogenic** |
| 2-year combined chronic toxicity/oncogenicity<br>(diet)<br>(RS)-methoprene<br><br><br>Sprague Dawley rat<br><br>PMRA #1229374 | NOAEL not established since histopathological examination was not conducted at dose levels.<br><br>LOAEL = 5000 ppm (250 mg/kg bw/day) (HDT)<br>Effects at the LOAEL: ↑incidence of hepatic lesions [slight bile-duct proliferation and very slight to slight portal lymphocyte infiltration] (♂); ↑liver wt (♀)<br><br>**Not oncogenic** |
| **Developmental/Reproductive Toxicity Studies** | |
| 3-generation reproduction<br>(diet)<br>(RS)-methoprene<br><br><br>Long Evans rat<br><br>PMRA #1229373 | Effect levels not established<br><br>Effects at ≥500 ppm (25 mg/kg bw/day): ↓pup wt in F3 on PND 4<br><br>Effects at 2500 ppm (125 mg/kg bw/day): Slightly ↓bwg noted in parental animals of the F0 and F1 generation, ↓pup wt in F3 on PND 14 & 21<br><br>**No adverse effects on the ability to reproduce**<br><br>**Supplemental (Non-guideline study)**<br>Limitations included: Necropsies were not conducted on any of the parental animals, or the F1 and F2 offspring (only the F3 offspring were necropsied at weaning). Parental reproductive organs were not examined. Organs were not weighed. Histopathological examination not conducted. |

| | |
|---|---|
| Developmental toxicity<br>(gavage)<br>(RS)-methoprene<br><br>Japanese rabbit<br><br>PMRA #1229376 | **Maternal toxicity**<br>NOAEL = 200 mg/kg bw/day<br>LOAEL = 2000 mg/kg bw/day<br>Effects at the LOAEL: ↑abortions (2/10 dams; day of abortions not reported), ↓bwg (38%)<br><br>**Developmental toxicity**<br>NOAEL = 200 mg/kg bw/day<br>LOAEL = 2000 mg/kg bw/day<br>Effects at the LOAEL: ↑abortions<br><br>**Abortions occurred at a dose considered to be in excess of the limit dose of testing. No evidence of increased sensitivity of the young. No malformations.** |
| Developmental toxicity<br>(gavage)<br>(RS)-methoprene<br><br>ICR mouse<br><br>PMRA #1229377 | **Maternal toxicity**<br>NOAEL = 600 mg/kg bw/day (HDT)<br>LOAEL not established<br><br>**Developmental toxicity:**<br>NOAEL = 600 mg/kg bw/day (HDT)<br>LOAEL not established<br><br>**Offspring toxicity:**<br>NOAEL =600 mg/kg bw/day (HDT)<br>LOAEL not established<br><br>**No evidence of increased sensitivity of the young. No malformations**<br><br>**Note**: A subset of the maternal animals at each dose level was allowed to deliver and rear their young for 3 weeks. During this time, litter weight, auricle development, hair growth, and opening of eyelids was recorded. Weanlings from 5 litters in each group were inspected for behavioural changes and external abnormalities at 21 days and necropsied. Remaining weanling mice were maintained for 7 weeks (weighed weekly, examined for sexual development and sacrificed/necropsied at 70 days old). |

| Genotoxicity studies | |
|---|---|
| Bacterial mutation assay<br>(S)-methoprene<br><br>Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538<br><br>PMRA #1233608 | Negative |
| Bacterial mutation assay<br>(RS)-methoprene<br><br>Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538<br><br>PMRA #1229382 | Negative |
| Mitotic recombination assay<br>(S)-methoprene<br><br>Saccharomyces cerevisiae D7<br><br>PMRA #1233609 | Negative |
| Dominant lethal study<br>(single or repeated intraperitoneal injection)<br>(RS)-methoprene)<br><br>Rat (albino, strain not specified)<br><br>PMRA #1229381 | Negative<br><br>Males that received 200 and 2000 mg/kg bw lost bw.<br>At 2000 mg/kg bw, only 2/5 ♂ survived after receiving two daily doses. |
| Mammalian cell mutation in vitro<br>(RS)-methoprene<br><br>Mouse lymphoma L5178Y cells<br><br>PMRA #2338851 | Negative |

| | |
|---|---|
| Mouse micronucleus in vivo<br>(RS)-methoprene<br><br>CD-1 mice<br><br>PMRA #2338852 | Negative |
| Chromosomal aberrations in vitro<br>(RS)-methoprene<br><br>Chinese hamster ovary (CHO) cells<br><br>PMPR (2001) | Negative |
| **Special Studies (non-guideline)** | |
| Endocrine activity in immature ♀ mice and castrated or bilaterally adrenalectomized ♂ rats<br><br>(Subcutaneous dosing)<br>(RS)-methoprene<br><br>PMPR (2001) | No increase in relative uterus weight was observed in mice following 3 days of dosing.<br><br>No increase in relative weights of seminal vesicles, ventral prostate or levator ani were observed in castrated rats following 7 days of dosing.<br><br>No effect on relative thymus weight was observed in bilaterally adrenalectomized rats following 6 days of dosing. |
| Acute oral toxicity<br><br>11-hydroxy-3,7,11-trimethyldodeca-2,4-dienoic acid<br>(animal and plant metabolite)<br><br>CD rat<br><br>PMPR (2001) | $LD_{50}$ > 6810 mg/kg bw<br><br>Rats at all doses displayed depression, and salivation was observed at 4.64 and 6.81 g/kg bw. |

| | |
|---|---|
| Acute oral toxicity<br><br>(11-methoxy-3,7,11-trimethyldodeca-2,6-dienoic acid (animal and plant metabolites)<br><br>CD rat<br><br>JMPR (2001) | $LD_{50}$ = 6810 mg/kg bw (♂)<br>$LD_{50}$ = 4870 mg/kg bw (♀)<br><br>Rats at all doses displayed depression, and salivation and convulsions were observed at 4.68 and 6.81 g/kg bw. |
| Acute oral toxicity<br><br>Isopropyl-11-hydroxy-3,7,11-trimethyldodeca-2,6-dienoate (animal and plant metabolites)<br><br>Sprague Dawley rat<br><br>JMPR (2001) | $LD_{50}$ > 8910 mg/kg bw (♂)<br>$LD_{50}$ = 8200 mg/kg bw (♀) |
| Acute oral toxicity<br><br>7-Hydroxycitronellic acid (plant metabolites)<br><br>Sprague Dawley rat<br><br>JMPR (2001) | $LD_{50}$ > 5000 mg/kg bw |
| Acute oral toxicity<br><br>7-methoxycitronellal (plant metabolites)<br><br>Sprague Dawley rat<br><br>JMPR (2001) | $LD_{50}$ > 5000 mg/kg bw |

| | |
|---|---|
| Acute oral toxicity<br><br>7-methoxy citronellic acid (animal and plant metabolite)<br><br>Rat (strain not specified)<br><br>IN4PR (2001) | $LD_{50}$ > 11,000 mg/kg bw (♂)<br>$LD_{50}$ = 7763 mg/kg bw (♀) |
| Eye irritation<br><br>7-methoxycitronellal (plant metabolite)<br><br>%ZW rabbits<br><br>IN4PR (2001) | Transient, mild conjunctival irritation (redness, chemosis and discharge) in all animals and a slight dulling of the corneal surface in one animal. The signs of ocular irritation disappeared within 2-3 days. |
| Dermal irritation<br><br>7-methoxycitronellal (plant metabolite)<br><br>%ZW rabbits<br><br>IN4PR (2001) | No irritation was observed in the animals with intact skin.<br>Very slight erythema and edema were observed in the animals with abraded skin.<br><br>It was noted that no control groups were included in the study. |
| Disruption of hepatic mitochondrial bioenergetics (in vitro)<br><br>INRR & (2008?) | Mitochondria were isolated from the livers of rats and features of mitochondrial physiology were characterized in the presence of methoprene.<br><br>Methoprene interferences with hepatic mitochondrial function occurred only at high concentrations. |

**Table 3 Toxicology Endpoints for Use in Health Risk Assessment for (S)-methoprene**

| Exposure Scenario | Study | Point of Departure and Endpoint | CAF[1] or Target MOE |
|---|---|---|---|
| Acute dietary general population | Not required as there were no effects in the database that were attributable to an acute exposure | | |
| Repeated dietary | 90-day rat dietary | NOAEL = 17 mg/kg bw/day (increased incidence of renal tubular regeneration observed in males at the LOAEL of 35 mg/kg bw/day) | 300 |
| | ADI = 0.06 mg/kg bw/day | | |
| Short- and intermediate-term dermal[2] | 90-day rat dietary | NOAEL = 17 mg/kg bw/day (increased incidence of renal tubular regeneration observed in males at the LOAEL of 35 mg/kg bw/day) | 300 |
| Short- and intermediate-term inhalation[3] | 90-day rat dietary | NOAEL = 17 mg/kg bw/day (increased incidence of renal tubular regeneration observed in males at the LOAEL of 35 mg/kg bw/day) | 300 |
| Cancer | A cancer risk assessment was not required as there was no evidence of oncogenicity | | |

[1] CAF (composite assessment factor) refers to a total of uncertainty and *Pest Control Products Act* factors for dietary assessments; MOE refers to a target MOE for occupational assessments

[2] Since an oral NOAEL was selected, a dermal absorption factor of 100% (default value) was used in a route-to-route extrapolation

[3] Since an oral NOAEL was selected, an inhalation absorption factor of 100% (default value) was used in route-to-route extrapolation

**Table 4 Integrated Food Residue Chemistry Summary**

| NATURE OF THE RESIDUE IN LAYING HEN | | PMRA # 2194869, 2194870 |
|---|---|---|
| Laying hens were dosed orally once with [5-$^{14}$C]-methoprene at 0.6-77 mg/kg bw. Samples of excreta, expired air, and eggs were collected for 14 days. Hens were euthanized for tissue sampling and analysis 2 and 14 days after dosing. | | |
| **Matrices** | **[5-$^{14}$C]-methoprene (Highest doses: 60-77 mg/kg bw)** | |
| | **TRRs (ppm)** | **% of Administered Dose** |
| Excreta (urine and feces) | - | 44-59 |
| Muscle (breast) | 12.0 | - |
| Fat | 7.6 | - |
| Liver | 152.4 | - |
| Eggs | - | 3-13 (majority in yolk) |
| Respired air | - | 21-33 |
| Data shown above for laying hen are for first 48 hours following a single dose at the highest dosing levels (60-77 mg ai /kg bw). | | |

| Metabolites identified | Major Metabolites (>10% of the TRRs) | Minor Metabolites (<10% of the TRRs) |
|---|---|---|
| **Radiolabel Position** | **[5-$^{14}$C]-methoprene** | |
| Feces | (RS)-Methoprene | Metabolites 1, 2, and 3 |
| Urine | - | Conjugates of Metabolites 2 and 3 |
| Blood | - | Cholesterol, Cholesteryl esters |
| Egg yolk | Triglycerides and Triglyceride with Metabolite 10 | (RS)-Methoprene, Metabolites 1-6 and 10, Cholesterol, Di- and Tri-glycerides with Metabolite 11, Diglyceride with Metabolite 10 |
| Liver | Cholesteryl with Metabolite 10 | (RS)-Methoprene, Metabolites 1-6, 10, and 11, Triglyceride, Cholesterol, Triglyceride with Metabolites 10 and 11 |
| Fat | (RS)-Methoprene, Triglycerides with Metabolite 10, Triglycerides | Metabolites 1-6, Cholesterol |
| Muscle (breast) | - | (RS)-Methoprene, Metabolites 1-6 |
| A majority of the [5-$^{14}$C]-methoprene dose was eliminated in feces and urine. In feces, unchanged parent was the major metabolite. [5-$^{14}$C]-methoprene was also significantly respired in air. Egg yolk retained a significant amount of the applied dose (3-13 %), which was mostly incorporated into triglycerides, diglycerides, and cholesterol which formed conjugates with primary metabolites. (RS)-Methoprene was a predominant residue in fat but only traces were identified in egg yolk, liver, and muscle. | | |

| **NATURE OF THE RESIDUE IN LACTATING COW** | **PMRA # 2194868, 2194871** |
|---|---|

One lactating cow was dosed orally once with [5-$^{14}$C]-methoprene at 0.61 mg ai/kg bw. Samples of urine, feces, milk, and respired air was collected over 7 days. Blood was sampled 6 h, 48 h, and 7 days following dosing. The cow was euthanized after 7 days.

| **Matrices** | **[5-$^{14}$C]-methoprene** | |
|---|---|---|
| | **TRRs (ppm)** | **% of Administered Dose** |
| Urine[1] | 41 | 20 |
| Feces[1] | 63 | 30 |
| All Tissues[2] | 9.19 | 4.5 |
| Milk[1] | 15.8 | 7.6 |
| Expired Air[1] | - | 15 |

[1]Cumulative for 7 days following single dose, [2]Corresponding to analysis following sacrifice 7 days following single dose.

| Metabolites identified | Major Metabolites (>10% of the TRRs) | Minor Metabolites (<10% of the TRRs) |
|---|---|---|
| **Radiolabel Position** | **[5-$^{14}$C]-methoprene** | |
| Milk[3] | Lactose | Lactalbumin, Casein, Methoprene |
| [3]Milk was analyzed at 44 h sampling where residues had peaked. | | |
| Radioactive residues from a single oral dose of [5-$^{14}$C]-methoprene was primarily eliminated in urine, feces, milk, and expired air (70.1 % applied dose). All tissues retained 4.5 % of the applied dose. Only milk was further analyzed. Results show that(RS)-methoprene had broken down and become incorporated into lactose, lactalbumin, and casein with low levels of (RS)-methoprene remaining. | | |

| **NATURE OF THE RESIDUE IN STEER** | **PMRA # 2194868, 2194870** |
|---|---|
| One steer was dosed orally once with [5-$^{14}$C]-methoprene at 7.2 mg ai/kg bw. Samples of urine, feces, and blood were collected for two weeks, air samples were obtained over 10 days. After 14 days, the steer was sacrificed and samples of fat, muscle, liver, lung, blood, and bile were obtained. Air samples were analyzed qualitatively rather than quantitatively. | |

| **Matrices** | **[5-$^{14}$C]-methoprene** | |
|---|---|---|
| | **TRRs (ppm)** | **% of Administered Dose** |
| Urine[1] | - | 22 |
| Feces[1] | - | 39 |
| Bile[2] | 51 | 0.2 |
| Gall bladder[2] | 20 | 0.03 |
| All Other Tissues[2] | - | 3.0 |
| [1]Cummulative for 14 days following single dose; [2]Corresponding to analysis following sacrifice 14 days following single dose. | | |

| Metabolites identified | Major Metabolites (>10% of the TRRs) | Minor Metabolites (<10% of the TRRs) |
|---|---|---|
| **Radiolabel Position** | **[5-$^{14}$C]-methoprene** | |
| Urine[3] | - | Metabolites 1, 2, 3, and 4 |
| Feces[4] | (RS)-Methoprene, Metabolites 1 and 3 | Metabolites 2 and 4 |
| Liver | Cholesterol | - |
| Fat | Cholesterol | - |
| Muscle | Cholesterol | - |
| Lung | Cholesterol | - |
| [3]Urine sample was 6 h post treatment. [4]Feces sample was 36-72 h post treatment. | | |

Metabolism of [5-$^{14}$C]-methoprene in a steer following a single oral dose, indicates that radioactive residues are mainly eliminated in feces (39 % applied dose) as unchanged parent and primary metabolites. Unchanged parent was not identified in urine, liver, fat, muscle, or lung. However, radioactive residues were also significantly eliminated in urine (22 % applied dose). (RS)-Methoprene was significantly taken up as cholesterol in liver, fat, muscle, and lung (>10 % TRRs).

Therefore, [5-$^{14}$C]-methoprene is primarily eliminated as unchanged parent in feces, and the small quantities taken up in tissue (cumulatively ~3 % applied dose) is incorporated into natural constituents (for example, cholesterol).

**Proposed Metabolic Scheme in Livestock**

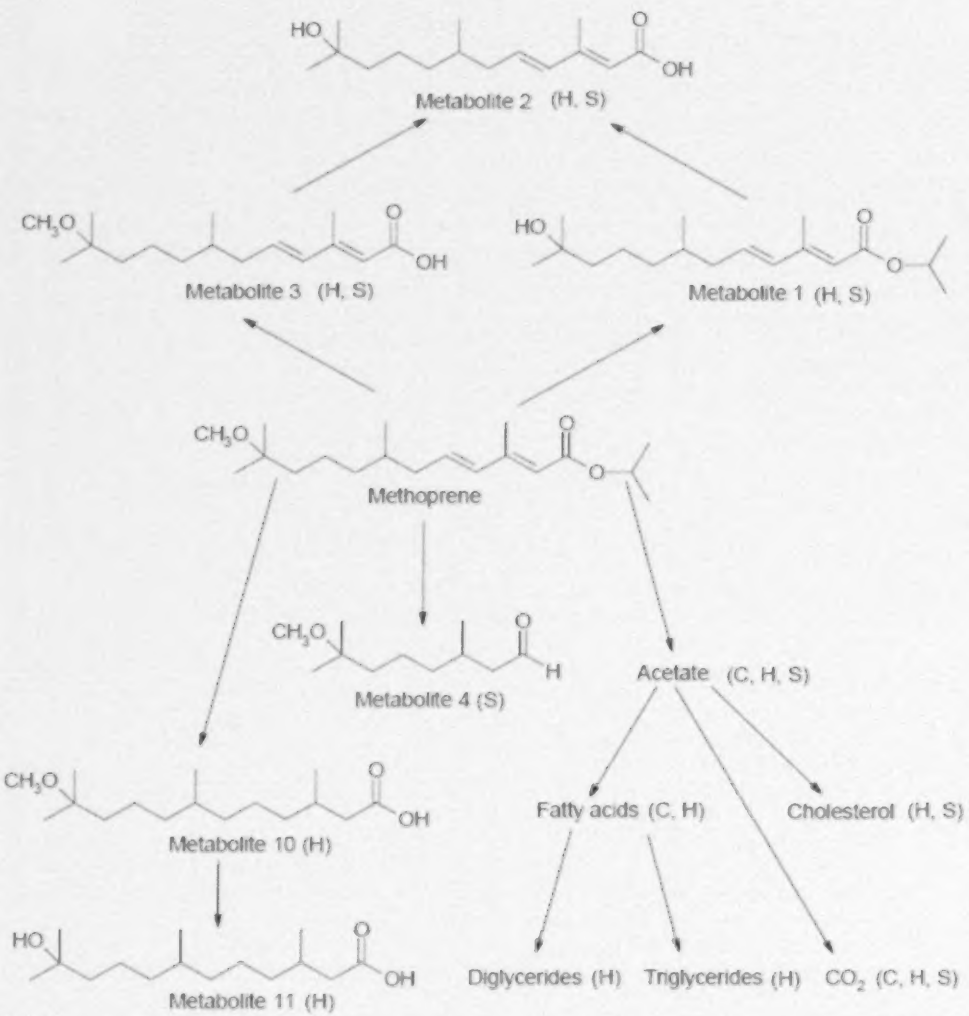


Figure 1. Proposed metabolic pathways for methoprene in animals (C = cow, H = hen, S= steer).

| **FREEZER STORAGE STABILITY** | **PMRA # 2194959** |
|---|---|

**Animal matrices: Milk, hamburger, chicken**

The freezer storage stability data for milk indicate that residues of (RS)-methoprene are stable -20°C for 50 days.

(S)-Hydroprene, which has similar structure and properties as (S)-methoprene, was shown to be stable in hamburger and chicken for 15 and 7 days, respectively, at -15°C.

| LIVESTOCK FEEDING – Dairy cattle | | PMRA # 2194963 |
|---|---|---|
| Lactating dairy cows were administered (RS)-methoprene at dose levels of 0.1, 0.3, and 1.0 ppm (RS)-methoprene in their feed for 28 consecutive days. The dose levels of 0.1, 0.3, and 1.0 ppm in feed represent 0.1x, 0.4x, and 1.2x the supported feeding level of (S)-methoprene to beef cattle. | | |
| **Commodity** | **Feeding Level (ppm)** | **Residues (ppm)** |
| Fat | 1.0 | <0.01-0.096 |
| Liver | | 0.016-0.021 |
| Kidney | | <0.01-0.016 |
| Muscle | | <0.01 |

**Table 5 Food Residue Chemistry Overview of Metabolism Studies and Risk Assessment**

| ANIMAL STUDIES | | |
|---|---|---|
| **ANIMALS** | | **Ruminant and Poultry** |
| **RESIDUE DEFINITION FOR ENFORCEMENT** | | (RS)-methoprene |
| **RESIDUE DEFINITION FOR RISK ASSESSMENT** | | (RS)-methoprene |
| **METABOLIC PROFILE IN ANIMALS (goat, hen, rat)** | | Metabolism in goat, hen, rat is similar |
| **FAT SOLUBLE RESIDUE** | | Yes |
| **DIETARY RISK FROM FOOD** | | |
| | **POPULATION** | **ESTIMATED RISK % of ACCEPTABLE DAILY INTAKE (ADI)** |
| | | **Food Alone** |
| **Basic chronic non-cancer dietary exposure analysis**<br><br>**ADI = 0.06 mg/kg bw/day** | **All infants < 1 year** | <1% |
| | **Children 1–2 years** | <1% |
| | **Children 3 to 5 years** | <1% |
| | **Children 6–12 years** | <1% |

| | | |
|---|---|---|
| | **Youth 13–19 years** | <1% |
| | **Adults 20–49 years** | <1% |
| | **Adults 50+ years** | <1% |
| | **Females 13-49 years** | <1% |
| | **Total population** | <1% |

# Appendix II Supplemental Maximum Residue Limit Information—International Situation and Trade Implications

(RS)-Methoprene is exempt from Tolerances in the the United States when used as a larvicide.

Table 1 compares the MRLs proposed for (RS)-methoprene in Canada with corresponding Codex MRLs[10]. A listing of established Codex MRLs is available on the Codex Alimentarius Pesticide Residues in Food website, by pesticide or commodity.

**Table 1 Comparison of Canadian MRLs and Codex MRLs (where different)**

| Food Commodity | Canadian MRL (ppm) | Codex MRL (ppm) |
|---|---|---|
| Cattle meat | 0.01 | 0.2 |

MRLs may vary from one country to another for a number of reasons, including differences in pesticide use patterns and the locations of the field crop trials used to generate residue chemistry data. For animal commodities, differences in MRLs can be due to different livestock feed items and practices.

[10] *The Codex Alimentarius Commission is an international organization under the auspices of the United Nations that develops international food standards, including MRLs.*

# References

## A. List of Studies/Information Submitted by Registrant

### 1.0 Chemistry


1447798 2003, Product Identification, DACO: 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9 CBI

1447799 2002, Manufacturing Facilities Qualification and Analyses of (S)-Methoprene technical Active Ingredient 1995-2002., DACO: 2.12.1, 2.13.3 CBI

2338849 2013, Five Batch Analysis of Technical S-methoprene, DACO: 2.13.3 CBI

2374836 2013, DACO 2 13 3 Batch Data response-22nov2013, DACO: 2.13.3 CBI

2194914 2012, Part 3 Chemistry Requirements for the Registration of an End-Use Product, DACO: 3.1.1, 3.1.2, 3.1.3, 3.1.4, 3.5.11, 3.5.12, 3.5.13, 3.5.15, 3.5.4, 3.5.5, 3.5.6, 3.5.7, 3.5.8, 3.5.9

2194915 2004, RF2038 Granule Description of the Starting Materials, Production and Formulation Process, DACO: 3.2.1, 3.2.2, 3.2.3 CBI

2194917 2004, Validation of a Chemical Analysis Procedure for the Assay of the Active Ingredient in RF2038 Granule, DACO: 3.4.1, 3.4.2 CBI

2194918 2004, Product Chemistry of RF2038 Granule, DACO: 3.5.1, 3.5.2, 3.5.3, 3.5.6 CBI

2194919 2006, Storage Stability and Package Compatibility of RF 2982, DACO: 3.5.10, 3.5.14 CBI

2338857 2009, Formulation process for 2% (S)-Methoprene Molasses Based Cattle Feed Concentrate, DACO: 3.2.2 CBI

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**B. Additional Information Considered**

**i) Published Information**

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